

A prospective cohort study in non-hospitalized household contacts with SARS-CoV-2 infection: symptom profiles and symptom change over time

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Summary: At the time of diagnosis, non-hospitalized household contacts with laboratory-confirmed SARS-CoV-2 infection most commonly had upper respiratory (68%) and neurologic (64%) symptoms; few (19%) reported fever; 17% were asymptomatic; 4% had recently resolved illness and 13% subsequently developed symptoms.

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Abstract

Background. Improved understanding of SARS-CoV-2 spectrum of disease is essential for clinical and public health interventions. There are limited data on mild or asymptomatic infections, but recognition of these individuals is key as they contribute to viral transmission. We describe the symptom profiles from individuals with mild or asymptomatic SARS-CoV-2 infection.

Methods. From March 22 to April 22, 2020 in Wisconsin and Utah, we enrolled and prospectively observed 198 household contacts exposed to SARS-CoV-2. We collected and tested nasopharyngeal (NP) specimens by RT-PCR two or more times during a 14-day period. Contacts completed daily symptom diaries. We characterized symptom profiles on the date of first positive RT-PCR test and described progression of symptoms over time.

Results. We identified 47 contacts, median age 24 (3-75) years, with detectable SARS-CoV-2 by RT-PCR. The most commonly reported symptoms on the day of first positive RT-PCR test were upper respiratory (n=32, 68%) and neurologic (n=30, 64%); fever was not commonly reported (n=9, 19%). Eight (17%) individuals were asymptomatic at the date of first positive RT-PCR collection; two (4%) had preceding symptoms that resolved and six (13%) subsequently developed symptoms. Children less frequently reported lower respiratory symptoms (age <18: 21%, age 18-49: 60%, age 50+ years: 69%; p=0.03).

Conclusions. Household contacts with lab-confirmed SARS-CoV-2 infection reported mild symptoms. When assessed at a single time-point, several contacts appeared to have asymptomatic infection; however, over time all developed symptoms. These findings are important to inform infection control, contact tracing, and community mitigation strategies.

Key words: COVID-19 symptoms, SARS-CoV-2, community

INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the virus responsible for coronavirus disease 2019 (COVID-19), continues to cause significant morbidity and mortality worldwide [1, 2].

Rapid recognition of COVID-19 symptoms is vital for timely clinical diagnosis, management, and for public health interventions such as contact tracing activities and infection prevention and control measures. Understanding the frequency of asymptomatic infections in the community setting is also important to inform mitigation efforts focused on reducing viral transmission.

As the COVID-19 pandemic progresses, our understanding of the clinical spectrum of COVID-19 is quickly evolving. However, the majority of our current information on the clinical presentation of COVID-19 comes from patients requiring hospitalization [3-5] and from special populations such as those in outbreak investigations (e.g., cruise ships) that only capture symptom information at a single point in time [6-9] and in long-term care facilities [10]. While the clinical characteristics and symptoms of individuals with more severe COVID-19 have been described, there remains relatively little detailed information on the natural progression of clinical and symptom profiles for individuals with mild illness, or people with no symptoms but laboratory evidence of infection. Here we describe a cohort of household members (hereafter referred to as household contacts) who tested positive for SARS-CoV-2 following exposure to someone else in their home with laboratory-confirmed infection. We describe their demographic and clinical characteristics, time from exposure to symptom onset, symptom profiles, and the evolution of symptoms over time.

METHODS

Study population

Individuals with COVID-19 identified through routine public health surveillance and their household contacts were enrolled in a household transmission investigation. We enrolled households from March 22 to April 22, 2020, in the Milwaukee, Wisconsin and Salt Lake City, Utah metropolitan areas, as previously described in detail (N. Lewis, V. Chu, D. Ye, et al., manuscript in preparation). Only the household contacts of source individuals were included as the study population for this analysis; no household contacts were hospitalized prior to or during the 14-day study period.

Data collection and confirmatory testing

We interviewed household contacts using a standardized questionnaire to obtain demographic and clinical characteristics, along with detailed symptoms that contacts may have experienced prior to enrollment as well as symptoms experienced on the day of enrollment. On the first day of the study period (day 0, i.e. day of enrollment), we collected nasopharyngeal (NP) swab specimens from all 198 enrolled household contacts. We observed household contacts for 14 days following enrollment and requested that they record daily measured temperatures and symptoms in a symptom diary. On day 14 (the final close-out visit), we returned to the household and collected NP swab specimens from all household members and retrieved the daily symptom diaries. During the 14-day follow-up, an investigation team returned to the household for interim NP swab collections from all household contacts if any previously asymptomatic household contact developed new symptoms. We tested NP specimens using the CDC 2019-nCoV real-time polymerase chain reaction (RT-PCR) assay [11]. Contacts with SARS-CoV-2 infection confirmed by RT-PCR on at least one NP were included in this analysis.

Analyses

We assessed symptoms reported by household contacts on the collection date of their first RT-PCR-positive NP specimen (Figure 1, Subset A), and categorized symptoms as constitutional (fever, chills, myalgia, or fatigue), upper respiratory (runny nose, nasal congestion, or sore throat), lower respiratory (cough, difficulty breathing, shortness of breath, wheezing, or chest pain), neurologic (headache, loss of taste, or loss of smell), and gastrointestinal (nausea/vomiting, diarrhea, or abdominal pain). We calculated proportions for each category of symptoms and stratified these proportions by sex, age, race, ethnicity and presence of self-reported underlying medical conditions. Underlying medical conditions included diabetes mellitus, immunocompromising conditions, and any chronic lung, cardiovascular, kidney, liver, neurologic, or other chronic disease. We also evaluated the co-occurrence of various symptom combinations. Differences between groups were assessed using a Fisher's exact test.

We identified and prospectively followed household contacts who were asymptomatic at the time they initially tested positive for SARS-CoV-2 by PCR (Figure 1, Subset B) to see if they developed symptoms during the study period. We also reviewed symptom data to identify any prior symptoms. To examine evolution of symptoms over time, we described in detail the symptom diaries of a subset of household contacts who were negative on enrollment (day 0) but tested positive for SARS-CoV-2 during the two-week longitudinal follow-up period (Figure 1, Subset C). Limiting this part of the analysis to this subset of positive contacts ensured their reported symptoms were likely due to acute COVID-19 and allowed for a granular description of day-by-day symptom evolution.

We used a survival function to estimate the median days from exposure, defined as symptom onset in household source cases, to symptom onset in the corresponding household contacts. We performed analyses using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA) and R-studio version 1.1.453 (RStudio Inc., Boston MA, USA). This protocol was reviewed by CDC human subjects research officials and the activity was deemed non-research as part of the COVID-19 public health response.

RESULTS

Of the 198 contacts enrolled, three withdrew, 47 tested RT-PCR positive at one or more sample collections and 148 remained negative during follow up (Figure 1). We included the 47 household contacts with an RT-PCR positive NP specimen in this analysis. Forty-two contacts (89%) were RT-PCR positive on day 0 and five (11%) changed from RT-PCR negative on day 0 to RT-PCR positive during follow-up. All household contacts (n=198, 100%) had complete symptom diary information on the collection date of first positive RT-PCR and most RT-PCR positive household contacts (n=37/47, 79%) had complete symptom diary information from the entire observation period.

Of the 47 household contacts with laboratory-confirmed SARS-CoV-2 infection by RT-PCR, the majority were female (n=29, 62%), white (n=35, 74%), non-Hispanic (n=42, 89%), and with a variable age distribution: <18 years (n=14, 30%); 18-49 years (n=20, 43%); 50-64 years (n=10, 21%); 65 years or older (n=3, 6%). Half (n=24, 51%) of the household contacts with SARS-CoV-2 had an underlying medical condition, with the most prevalent conditions being any chronic lung disease (n=9, 19%) and any cardiovascular disease (n=6, 13%) (Table 1). The proportion of contacts with one or more underlying medical condition increased with age (<18 years: n=4/14, 29%; 18-49 years: n=11/20, 55%; 50-64 years: n=6/10, 60%; 65+ years: n=3/3, 100%).

In Figure 2 we present symptoms reported on the date of first positive RT-PCR and symptoms reported throughout the illness for the 47 RT-PCR positive household contacts (see Supplemental Table for more detail). The most commonly reported symptom categories on the date of first positive RT-PCR were upper respiratory (n=32, 68%) followed by neurologic (n=30, 64%). For symptoms experienced throughout the illness, the percent of household contacts reporting neurologic symptoms increased to 94% (n=44), predominated by headache (n=41, 87%), followed by upper respiratory symptoms (n=42, 89%). Nasal congestion and runny nose were the most commonly reported upper respiratory symptoms at both date of first positive RT-PCR test (n=17, 47% and n=39, 83% respectively) and throughout the illness (n=20, 43% and n=32, 68% respectively).

Fewer than half (n=20, 43%) of household contacts reported cough at date of first positive RT-PCR which increased to 74% (n=35) reported at any time throughout the illness. A similar pattern was observed for difficulty breathing (n=5, 11% at date of first positive RT-PCR and n=19, 40% reported any time). Only 19% (n=9) of household contacts reported subjective or objective fever at date of first positive RT-PCR, although just over half (n=25, 53%) reported experiencing a fever at any time during the illness. Less than a quarter (n=11, 23%) of household contacts reported gastrointestinal symptoms at date of first positive RT-PCR, while over half reported having experienced gastrointestinal symptoms at any time (n=25, 53%). On the date of first positive RT-PCR, eight (17%) household contacts had no symptoms. Of these eight individuals, two (4%) individuals were post-symptomatic (prior symptoms had resolved by collection date of first positive PCR); the remaining six (13%) individuals were pre-symptomatic (i.e. developed symptoms during the follow-up observation period).

Symptoms on the date of first positive RT-PCR stratified by sex, age, comorbidity status, and race are shown in Figure 3 (and in more detail in Supplemental Table). A majority of both sexes reported upper respiratory or neurologic symptoms with no statistically significant differences found between the sexes. Similarly, contacts with and without underlying medical conditions most commonly reported upper respiratory or neurologic symptoms with no significant differences between the two groups. Among the different age groups, the most common symptoms were as follows: upper respiratory symptoms in children <18 years (n=10, 71%), neurologic symptoms in adults 18-49 years (n=14, 70%), and upper respiratory symptoms in adults 50 years or older (n=11, 85%). There was a significant difference in the percentage of household contacts reporting lower respiratory symptoms with increasing age (age <18 years: 21%, age 18-49 years: 60%, age 50+ years: 69%; Fischer's exact p=0.03).

Co-occurrence of the symptoms reported on the date of first positive RT-PCR is displayed in Figure 4. Among children <18 years of age, the most commonly reported symptom profiles on the date of first

positive RT-PCR were upper respiratory alone (n=3, 21%) or lack of symptoms (n=3, 21%). Among adult household contacts, the most commonly reported symptom profiles were as follows: six (18%) experienced at least one symptom in each category (constitutional, upper respiratory, lower respiratory, neurologic, and gastrointestinal) and five (15%) experienced no symptoms at date of first positive RT-PCR. No person presented with only constitutional or only gastrointestinal symptoms on the date of first positive RT-PCR (Figure 4).

The median duration of illness with any symptom was at least 16 days (IQR: 11-21); n=14, 30% of individuals were still symptomatic at study close-out. Among RT-PCR positive household contacts, 25% developed symptoms three days (95% CI: 2-4) after exposure (symptom onset in the presumed household source case) and the estimate increased to 50% at four days (95% CI: 3-5), and 75% at six days (95% CI: 5-9) post exposure. In addition, 50% of the household contacts tested positive by RT-PCR six days (95% CI: 5-7) after the onset of symptoms in the household contact, increasing to 75% at eight days (95% CI: 7-11).

Figure 5 shows symptoms relative to RT-PCR results for five contacts who were RT-PCR negative on day 0 and then positive during follow up (Individuals A-E), and six contacts who had no symptoms at collection date of first positive RT-PCR (Individuals F-K). Nearly all (n=10, 91%) contacts reported upper respiratory and/or neurologic symptoms, with longer overall duration observed for the upper respiratory symptoms. About a quarter of contacts (n=3, 27%) reported gastrointestinal symptoms; no gastrointestinal symptoms were reported in isolation, and all resolved within 72 hours of onset. Younger household contacts reported fewer symptoms overall, and when symptoms did occur, duration of illness tended to be shorter.

Of the eight (17%) individuals who did not have symptoms at the date of first positive RT-PCR, two (4%) had prior symptoms that resolved by collection date of first positive RT-PCR; the remaining six (13%) individuals developed symptoms during the follow up period, or are considered “pre-symptomatic” [five within 48 hours of positive RT-PCR collection, and one within five days].

DISCUSSION

The symptom profiles and demographic characteristics of our cohort of SARS-CoV-2 RT-PCR positive household contacts differ from those described in inpatient populations [3-5, 12]. Our findings indicate that mild upper respiratory and neurologic manifestations may be more common and findings such as fever and cough may be less common among the non-hospitalized population than previously appreciated. Additionally, we observed no continually asymptomatic individuals in our study; six (13%) individuals who had no symptoms at the collection date of first positive RT-PCR all went on to develop symptoms during follow up. This has important implications for diagnosis and community mitigation strategies such as clinical case definitions, symptom screening, temperature screening, testing, and return to school policies. Our findings also emphasize the importance of widespread preventative measures since individuals with mild symptoms are difficult to identify without testing but may still be a source for spread of infection.

We compared the demographic characteristics and symptom profiles of our cohort of household contacts to those of inpatients described by the COVID-19–Associated Hospitalization Surveillance Network (COVID-NET) [12]. We found that our population were younger (28% vs 75% age 55 years or older), less likely to be male (38% vs 54%), and had fewer individuals with one or more underlying health conditions (51% vs 89%) [12]. We compared our cohort's symptoms on date of first positive RT-PCR to the symptoms on day of admission described in COVID-NET; we found that our cohort was less likely to report cough (43% vs 86%), fever or chills (19% and 6% vs 85%), or difficulty breathing/shortness of breath (11% vs 80%). COVID-NET and additional studies have also described gastrointestinal symptoms in a significant proportion of hospitalized patients with COVID-19 [12-15] with COVID-NET reporting 27% and 24% of inpatients having diarrhea and nausea/vomiting, respectively [12]. In contrast only 13% of our cohort reported diarrhea, and 9% nausea/vomiting at collection date of first positive RT-PCR; 36% and 19% reported having ever had diarrhea or nausea/vomiting, respectively.

The symptoms that were most commonly reported by our cohort at the date of first positive RT-PCR were upper respiratory (primarily nasal congestion and runny nose), and neurologic (primarily headache). Only 19% of our cohort reported fever (subjective or objective) on the collection date of first positive RT-PCR and 53% reported ever having had fever during the 14-day observation period. When comparing symptom profiles by age group, we found that children under 18 years were more likely to be asymptomatic compared to persons 18 years or older, and symptomatic children were most likely to report upper respiratory symptoms. Several studies have noted that the inpatient COVID-19 population tends to be predominantly male, and that males have a higher morbidity and mortality when hospitalized for COVID-19 [12, 16]. However, we did not observe any statistically significant differences in reported symptoms stratified by sex.

We also identified a significant proportion of individuals (13%) who were asymptomatic on the collection date of first positive specimen. This proportion of asymptomatic individuals is similar to that found in other younger, more healthy populations such as navy service members where 20% of COVID-19 cases were asymptomatic [17]. However, it is important to note that all the asymptomatic individuals in our population went on to develop symptoms over the 14-day follow-up period. This is consistent with another longitudinal study that found only 2% of individuals who were asymptomatic at diagnosis remained asymptomatic throughout a 14-day observational period[18]. In contrast, a review of 16 COVID-19 observational studies found that 40-50% of individuals with COVID-19 were asymptomatic (although only 5 of the 16 cohorts provided longitudinal data); the five studies with longitudinal data found that very few asymptomatic individuals (~10-15%) went on to develop symptoms [19]. Notably, our prospective design included asking each contact about 18 different symptoms daily for 14 days. Other observational or retrospective studies likely identified symptoms differently, possibly less granular and/or sensitive. It is possible that individuals classified as asymptomatic in other studies may be classified as symptomatic using the methodology in our study. Understanding the spectrum of the natural history of COVID-19 is important, but even so,

there may continue to be challenges identifying COVID-19 cases early due to non-specific or mild symptoms.

The study findings presented here must be interpreted in light of several potential limitations. First, symptom data were self-report and may be subject to recall bias, when symptom onset preceded the day 0 visit. Also, symptoms are subjective by definition and hence individuals may experience and report symptoms differently. Second, by the time we reached the households, 89% of RT-PCR positive household contacts were already positive (i.e. positive by RT-PCR on day 0). Prior symptom data were captured but not recorded daily. To allow for a granular description of day-by-day symptom evolution we limited our sample to household contacts who were negative on enrollment (day 0) but tested positive for SARS-CoV-2 during the two-week longitudinal follow-up period. This ensured an accurate natural history was captured but reduced the sample size described. Third, there were two household contacts where symptoms had resolved by collection date of first positive RT-PCR, likely because we missed the date of first detectable virus by RT-PCR. Fourth, household contacts were selected by convenience sample and therefore are not representative of all US households.

We describe a cohort of household contacts with SARS-CoV-2 infection who have milder symptoms (upper respiratory and neurologic), fewer systemic signs of infection (fever), and who did not require hospitalization. These individuals would not be easily identified as having COVID-19 through common symptom criteria (fever, cough, shortness of breath) or temperature screening. Our findings can inform quarantine strategies for household contacts of individuals with SARS-CoV-2 infection and emphasize the importance of widespread use of community mitigation measures (social distancing, face coverings, respiratory hygiene) to stop the spread of disease by those with milder symptoms who go unidentified as having COVID-19. This is particularly important in younger populations where we identified higher proportions of pre-symptomatic individuals and individuals with milder symptoms. Because symptom and temperature screening alone will be inadequate to

identify all SARS CoV-2 infected persons, it is important that guidance concerning younger populations, such as return to school policies, emphasize widespread infection prevention and control measures (virtual learning, social distancing, face coverings, hand hygiene with either soap and water or a hand sanitizer , covering coughs and sneezing with a tissue, ensuring availability of adequate supplies of soap and hand sanitizers containing at least 60% alcohol, environmental cleaning and disinfection, and posting COVID-19 infographics in highly visible locations) [20-24]. Our findings of mild symptoms and a short duration from exposure to symptom onset (median of 4 days) can inform quarantine strategies for household contacts of individuals with SARS-CoV-2 infection.

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FIGURE LEGENDS:

Figure 1: Flowchart for household contacts enrolled in the study, by PCR testing results

*_aSubset A; _bSubset B; _cSubset C

Figure 2: COVID-19 symptoms reported by household contacts (n=47) on the date of 1st positive SARSCoV-2 RT-PCR test compared to symptoms reported throughout the illness

*Nasal congestion variable was present for 36/47 symptom diaries, denominator n=36 for these estimates. _bLoss of smell: partial n=7, 50% and complete n=7, 50%. _cLoss of taste: partial n=9, 64% and complete n=5, 36%. _dCough: dry n=12, 60% and productive n=8, 40% _eSubjective and objective

Figure 3: COVID-19 symptoms reported by household contacts on the date of 1st positive SARS-CoV-2 RT-PCR test, stratified by sex, age, underlying medical condition, and race (n=47)_a

*_aConstitutional = fever, chills, muscle aches, fatigue, Upper respiratory = runny nose, nasal congestion, sore throat, Lower respiratory = cough, discomfort in chest, shortness of breath, wheezing, chest pain, Neurologic = headache, loss of taste, loss of smell, Gastrointestinal = nausea, diarrhea, abdominal pain; _bOther race = American Indian/Alaska Native, Asian, Other; p-values calculated using Fisher's exact test

Figure 4: Combinations of COVID-19 symptoms reported by household contacts on the date of first positive SARS-CoV-2 RT-PCR test (n=47)_a

*_aConstitutional = fever, chills, muscle aches, fatigue, Upper respiratory = runny nose, nasal congestion, sore throat, Lower respiratory = cough, discomfort in chest, shortness of breath, wheezing, chest pain, Neurologic = headache, loss of taste, loss of smell, Gastrointestinal = nausea, diarrhea, abdominal pain

Figure 5. Timeline of symptom onset in household contacts who changed from negative for SARS-CoV-2 (by RT-PCR) on day 0 to positive during follow-up (n=5) and contacts who were asymptomatic at collection date of 1st positive specimen (n=6) but developed symptoms later

*_aFirst household exposure (defined as symptom onset in the household source case) to enrollment (day 0)

Table 1. Demographic and clinical characteristics of household contacts whose nasopharyngeal (NP) specimens tested positive or negative for SARS-CoV-2 by polymerase chain reaction [RT-PCR]^a

	SARS-CoV-2 RT-PCR Positive (n=47)	SARS-CoV-2 RT-PCR Negative (n=148)
Sex n (%)		
Male	18 (38%)	78 (53%)
Female	29 (62%)	70 (47%)
Age category (years) n (%)		
<18	14 (30%)	55 (37%)
18-49	20 (43%)	69 (47%)
50-64	10 (21%)	19 (13%)
65+	3 (6%)	5 (3%)
Race n (%)		
White	35 (74%)	109 (74%)
Black/African American	4 (9%)	22 (15%)
Asian	4 (9%)	10 (7%)
American Indian/Alaska Native	1 (2%)	3 (2%)
Native Hawaiian/Other Pacific Islander	0 (0%)	2 (1%)
Multiracial	3 (6%)	1 (1%)
Ethnicity n (%)		
Non-Hispanic	42 (89%)	121 (82%)
Hispanic	5 (11%)	27 (18%)
State of residence n (%)		
Utah	31 (66%)	100 (68%)
Wisconsin	16 (34%)	48 (32%)
Any underlying medical condition ^b n (%)	24 (51%)	39 (26%)
Any chronic lung disease	9 (19%)	26 (18%)
Any cardiovascular disease	6 (13%)	14 (9%)
Diabetes mellitus	4 (9%)	2 (1%)
Any chronic kidney disease	1 (2%)	1 (1%)
Any chronic liver disease	1 (2%)	1 (1%)
Any immunocompromising condition	2 (4%)	1 (1%)
Other	6 (13%)	4 (3%)

^a Data collection in Wisconsin and Utah household contact cohort, March 22–April 22, 2020. ^b Any chronic

lung disease = asthma, chronic obstructive pulmonary disease, or other chronic lung disease, any

cardiovascular disease = hypertension, coronary artery disease/myocardial infarction, or other

cardiovascular disease, any chronic kidney disease = end-stage renal disease, renal insufficiency, or

other kidney disease, any liver disorder = non-alcoholic fatty liver disease or other chronic liver

condition), any immunocompromising condition = human immunodeficiency virus, cancer, or other

immunosuppressive condition, and any other chronic conditions = anemia, psoriasis, thyroid

disorder

Figure 1

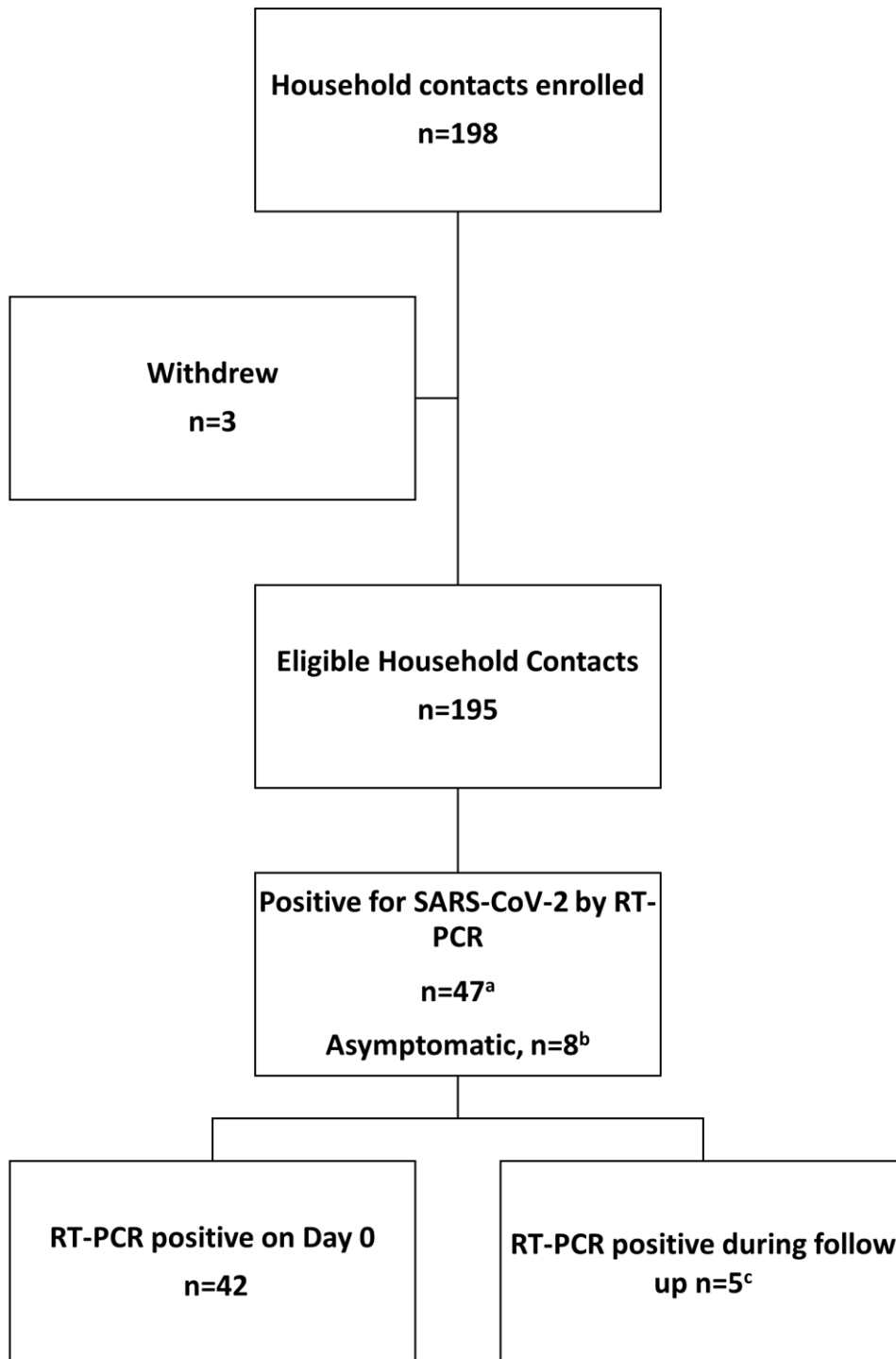
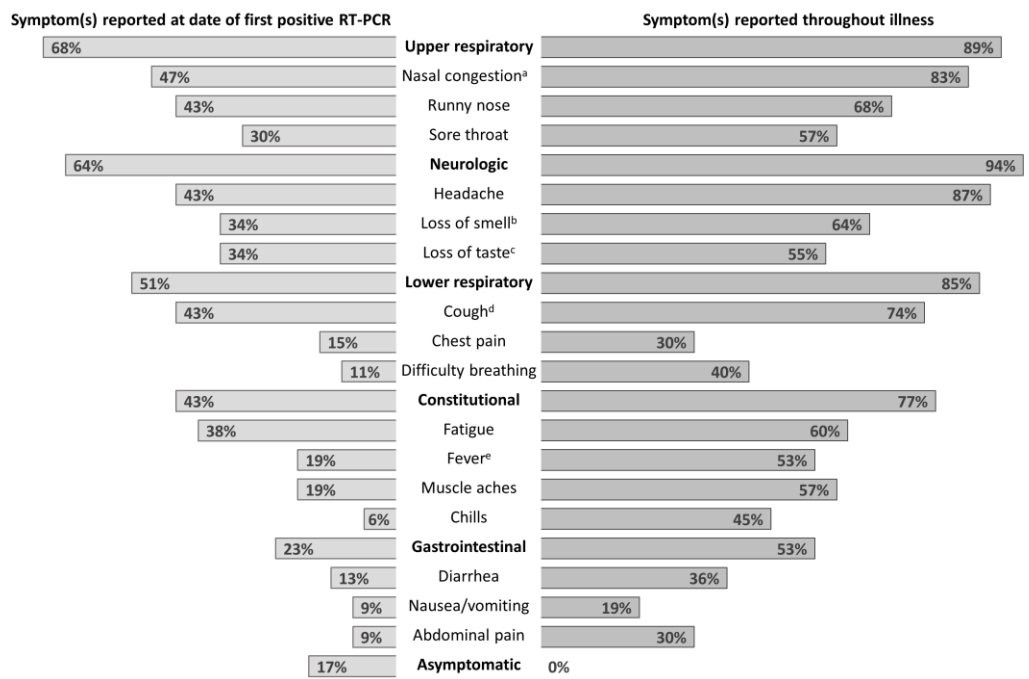
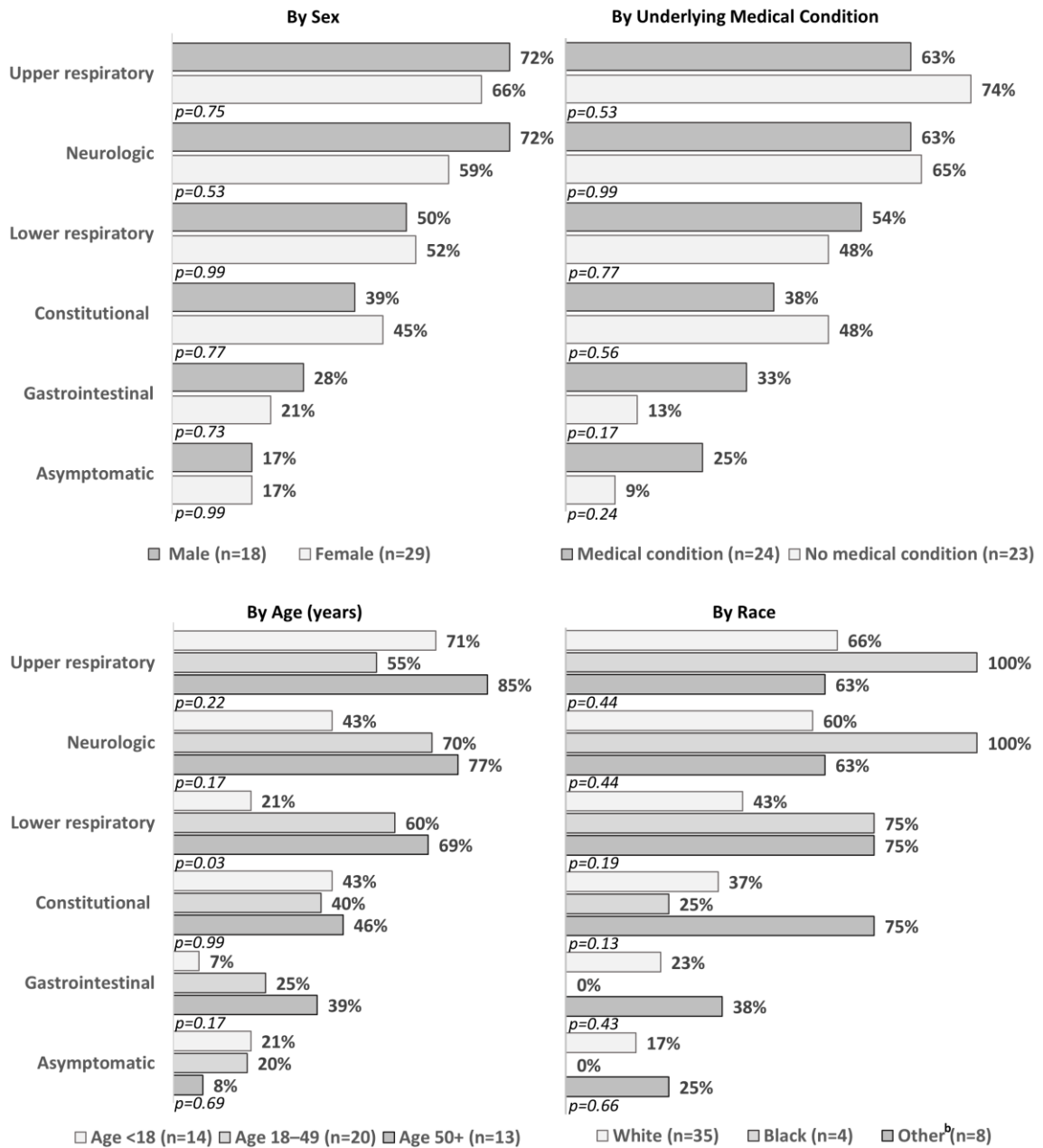


Figure 2



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Figure 3



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Figure 4

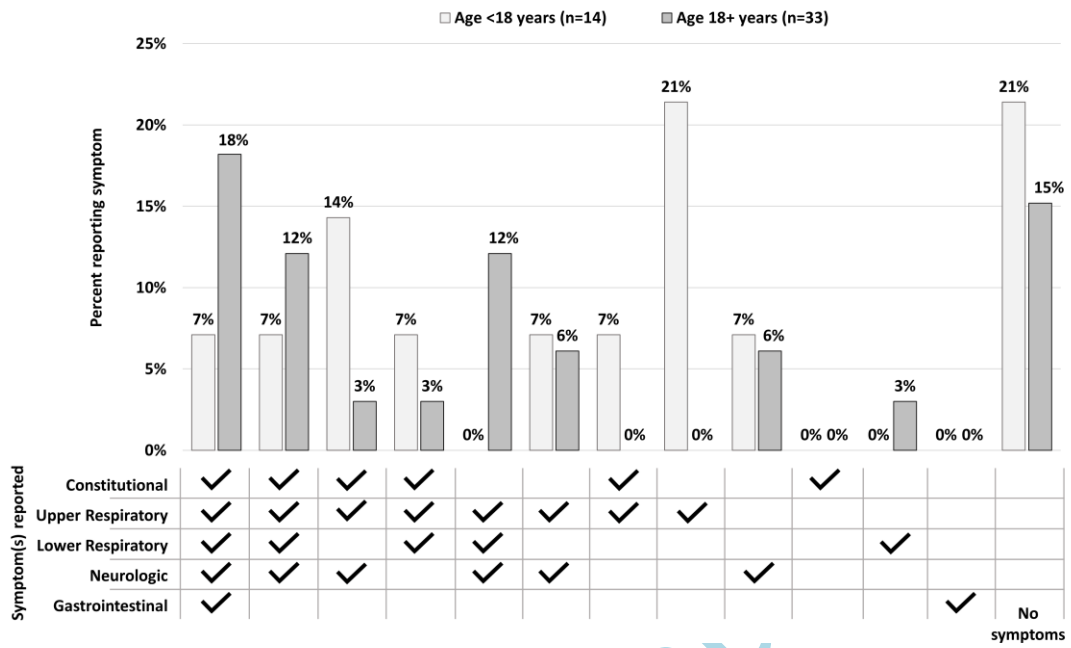


Figure 5

